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Risk of Oophorectomy After Hysterectomy

Dr. Elizabeth R. Casiano, MD, MS, Dr. Emanuel C. Trabuco, MD, MS, Dr. Adil E. Bharucha, MBBS, MD, Ms. Amy L. Weaver, MS, Ms. Cathy D. Schleck, BS, Dr. L. Joseph Melton III, MD, and Dr. John B. Gebhart, MD, MS

Division of Obstetrics and Gynecology (Dr. Casiano), University of Texas Health Science Center, San Antonio, Texas, and Division of Gynecologic Surgery (Drs. Trabuco and Gebhart), Division of Gastroenterology and Hepatology (Dr. Bharucha), Division of Biomedical Statistics and Informatics (Mss. Weaver and Schleck), and Division of Epidemiology (Dr. Melton), Mayo Clinic, Rochester, Minnesota

Abstract

Objective—To compare the risk of subsequent oophorectomy among women who had hysterectomy for benign indications and those who did not.

Methods—Using Rochester Epidemiology Project resources, we compared the risk of oophorectomy through December 31, 2008 among 4,931 Olmsted County, Minnesota, women who had ovary-sparing hysterectomy for benign indications (cases) between 1965 and 2002 and 4,931 age-matched women who did not have hysterectomy (referents). The cumulative incidence of subsequent oophorectomy was estimated by the Kaplan-Meier method, and comparisons were evaluated by Cox proportional hazard models using age as the time scale to allow for complete age adjustment.

Results—The median follow-up for cases and referents was 19.6 and 19.4 years, respectively. At 10, 20, and 30 years after hysterectomy, the respective cumulative incidence of subsequent oophorectomy was 3.5%, 6.2%, and 9.2% among cases and 1.9%, 4.8%, and 7.3% among referents. The overall risk of subsequent oophorectomy among cases was significantly higher than among referents (hazard ratio [HR], 1.20; 95% CI, 1.02–1.42; $P=.03$). Furthermore, among cases, the risk of subsequent oophorectomy was significantly higher (HR, 2.15; 95% CI, 1.51–3.07; $P<.001$) in women who had both ovaries preserved compared with those who initially had one ovary preserved.

Conclusion—The incidence of oophorectomy after hysterectomy is only 9.2% at 30-year follow-up and is only 1.9 percentage points higher than the incidence of oophorectomy in referent women with intact reproductive organs.

Introduction

Ovarian cancer causes 14,000 deaths annually in the United States (1). Performing blood-based screening tests or sonographic surveillance has failed to improve early detection or survival. Prophylactic oophorectomy at the time of benign hysterectomy prevents subsequent ovarian malignancy. However, in those at low risk for ovarian malignancy, the absolute risk of ovarian cancer among women after ovarian preservation during benign

Corresponding author: John Gebhart, MD, MS, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905.
gebhart.john@mayo.edu.

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hysterectomy is low (0.03%–1.96%) (2,3). A 24-year follow-up of the Nurses' Health Study revealed that only 34 of 13,035 women (0.3%) who had ovarian preservation at the time of hysterectomy later succumbed to ovarian cancer (4). Furthermore, a growing body of evidence suggests that prophylactic oophorectomy is associated with increased overall mortality, coronary heart disease, dementia, osteoporosis, and other cancer mortality (4–7).

Women with ovarian preservation are at risk for future oophorectomy (8). This risk ranged from 2.9% to 7.7% in previous studies (5,9,10). However, this information was derived from studies with short follow-up that were not population based and lacked a comparison group (10–12). Moreover, in some series, subsequent oophorectomy was prompted by additional screening tests (eg, pelvic ultrasound) and thus may not reflect the true natural history of disease. An accurate appraisal of this question is necessary to refine our understanding of the risk-benefit ratio of prophylactic oophorectomy. We compared the risk of oophorectomy in a large community cohort of women who had hysterectomy for benign indications with age-matched referent women with intact uteri. In addition, the risk of pelvic reoperation was compared in women with one ovary compared with both ovaries preserved during hysterectomy.

Materials and Methods

This study used the data resources of the Rochester Epidemiology Project, which links and indexes the medical records of virtually all medical providers who serve the population of Olmsted County, Minnesota, including Mayo Clinic and its affiliated hospitals (Rochester Methodist and Saint Marys) and the Olmsted Medical Center and its affiliated community hospital (13). Since these institutions provide nearly all medical care for the community, this resource results in a comprehensive source of both inpatient and outpatient information for population-based epidemiologic research (14). The Rochester Epidemiology Project captures virtually all individuals who have lived in Olmsted County from 1966 on. As of July 2009, the Rochester Epidemiology Project included information on 493,606 individuals and their respective medical records from 65 different health care providers (15). The vast majority of Olmsted County residents use the medical system, including 85% of women of all ages seen in the past 3 years and more than 90% of adults older than 70 years seen in the past year (16). According to statistics from 2000, the majority of Olmsted County residents are white (90.3%), which is similar to the remainder of Minnesota (89.4%) and higher than the United States overall (75.1%). In 2000, Olmsted County had a 2.7% black population and 2.4% Hispanic population (17).

After approval by the institutional review boards of both Mayo Clinic and Olmsted Medical Center, Rochester Epidemiology Project resources were used to identify all Olmsted County residents who underwent hysterectomy between January 1, 1965, and December 31, 2002 (18). The procedure type and indications were identified electronically, as were the route of hysterectomy, unilateral or bilateral ovarian preservation, the date of subsequent oophorectomy, and the date of last follow-up or death (18). As had been done previously, we randomly selected 100 women and manually compared the procedure type in the electronic medical record system to the procedure type listed in the surgical note; these two sources agreed in 83% of cases.

Of the 9,893 women with hysterectomy in this original cohort, 876 women (8.8%) who had not authorized the use of their medical records for research were excluded (19). We also excluded 914 women who had hysterectomy for malignant disease and 3,172 women who had no intact ovaries at the completion of their hysterectomy. The remaining 4,931 women ("cases") were included for further analysis. For each hysterectomy case, one matched woman ("referent") was randomly selected from all Olmsted County female residents born

within 1 year of a case and seen at Mayo Clinic or Olmsted Medical Center in the same year that her matched case underwent hysterectomy ("index date"). As of the index date, the referent had not undergone hysterectomy and had at least one intact ovary. For each case and referent, the date of subsequent oophorectomy and date of last follow-up or death prior to December 31, 2008, were obtained electronically. For each referent, the date of subsequent hysterectomy prior to December 31, 2008, was also obtained.

Analysis was carried out using the Statistical Analysis System (SAS Institute, Inc, Cary, North Carolina). The Kaplan-Meier method was used to estimate the cumulative incidence of oophorectomy (1 minus the probability of survival free of oophorectomy) after the index date. The duration of follow-up was calculated from the index date to the date of the subsequent oophorectomy; otherwise the follow-up was censored at the date of last follow-up. The influence of hysterectomy (case compared with referent) on the risk of subsequent oophorectomy was evaluated based on fitting a Cox proportional hazards model using age as the time scale to allow for complete age adjustment. The association was summarized by calculating the hazard ratio (HR) and 95% confidence interval (CI) using the model estimated coefficient and its standard error estimated by the model. As a secondary analysis, the follow-up for a referent woman was censored at the date of a subsequent hysterectomy if the hysterectomy preceded an oophorectomy or their last follow-up date.

Among the cases, influence of age and calendar year on the risk of subsequent oophorectomy was assessed on the basis of fitting standard Cox models using time since hysterectomy as the time scale. The HR for the association between ovarian preservation (unilateral compared with bilateral) and risk of subsequent oophorectomy was estimated from a Cox model, again using age as the time scale to allow for complete age adjustment.

Our power calculations were completed based on reviewing past work with a similar cohort. We assumed that approximately 4,500 women would undergo hysterectomy with preservation of one or both ovaries. Because the reported frequency of reoperation after preservation of one or both ovaries during hysterectomy ranges from 3% to 7.6% (12), we anticipated that between 135 and 342 cases would have subsequent oophorectomy. Based on a sample size of 4,500 hysterectomy cases and 4,500 age-matched referents, the study was predetermined to have 80% power to detect an HR greater than 1.5 if a total of 200 women had subsequent oophorectomy, using sample size and power calculations for the 2-sided log-rank test (with a type I error level of 5%), as proposed by Schoenfeld (20).

Results

Within this cohort of 4,931 hysterectomy cases and 4,931 age-matched referents, both ovaries were intact at the index date in 79.5% of cases and 98.3% of referents. The mean age at the index date was 42.9 years (standard deviation [SD], 11.7 years) in cases and 43.6 years (SD, 12.1 years) in age-matched referents (Table 1). Approximately 74% of cases had vaginal hysterectomy; myomatous uterus was the most common indication for surgery (29.5%). Among the hysterectomy cases, the median duration of follow-up was 19.6 years (interquartile range [IQR], 9.6–29.0 years; range, less than 0.1–43.5 years), during which time 315 women had oophorectomy. The referents had a median follow-up of 19.4 years (IQR, 9.7–28.9 years; range, less than 0.1–43.5 years), during which time 247 women had oophorectomy (89 oophorectomy only and 158 oophorectomy concurrent with hysterectomy). The cumulative incidence of subsequent oophorectomy was 3.5%, 6.2%, and 9.2%, respectively, among the cases and 1.9%, 4.8%, and 7.3%, respectively, among the referents at 10, 20, and 30 years after the index date (Figure 1). The overall risk of subsequent oophorectomy among the cases was higher than that in the referents (HR, 1.20; 95% CI, 1.02–1.42; $P=.03$). In a secondary analysis, the follow-up for a referent woman was

censored at the date of a subsequent hysterectomy. The result of the secondary analysis was similar to the primary analysis (HR, 1.22; 95% CI, 1.03–1.45; $P=.02$).

Among the cases, age at the time of hysterectomy was associated with the risk of subsequent oophorectomy (HR, 1.62 per 10-year increase in age; 95% CI, 1.50–1.75; $P<.001$). The risk of subsequent oophorectomy was also related to the calendar period when hysterectomy was performed; that is, higher (HR, 1.35 [95% CI, 1.26–1.45] per 5-year increase in the calendar year; $P<.001$) for women who had hysterectomy more recently.

Either one ovary (1,015 women; mean age, 40.7 years [SD, 10.1 years]) or both ovaries (3,916 women; mean age, 43.5 years [SD, 12 years]) were preserved at hysterectomy. Among women with one preserved ovary, the cumulative incidence of subsequent oophorectomy was 1.2% at 2 years, 2.8% at 10 years, and 4.0% at both 20 and 30 years (Table 2). Among women with both ovaries intact, the cumulative incidence was 0.7% at 2 years, 3.7% at 10 years, 6.8% at 20 years, and 10.6% at 30 years. Hence, women in whom both ovaries were preserved at hysterectomy had an increased risk of reoperation (HR, 2.15; 95% CI, 1.51–3.07; $P<.001$) relative to women who did not have both preserved (ie, had only one ovary preserved).

Discussion

Although the cumulative incidence of a subsequent oophorectomy was higher among the cases (3.5%, 6.2%, and 9.2%) than in the referent group (1.9%, 4.8%, and 7.3%) at 10, 20, and 30 years, respectively, the absolute risk showed a minimal difference (less than 2 percentage points at 20-year- and 30-year follow-up). Moreover, the cumulative incidence of reoperation if both ovaries were preserved was only 10.6% at 30-year follow-up. Our estimates of reoperation at 30 years are higher than the previously reported range of 2.9% to 7.7% (10–12). However, these studies had a shorter follow-up period (average duration of 4 years) and lacked a comparison group.

We theorize that disruption of ovarian blood flow as a result of hysterectomy may alter ovarian function, which could lead to adnexal pathology. In fact, menopause has been shown to occur earlier in premenopausal women having ovary-sparing hysterectomy (21,22). Alternatively, patients who undergo hysterectomy may have underlying conditions (eg, chronic pelvic pain) that predispose to subsequent surgery.

Approximately 75% of hysterectomies in this study were vaginal, which is higher than the proportion (30–35%) reported elsewhere in the United States (23,24). In general, it is easier to perform an oophorectomy during abdominal than vaginal hysterectomy. However, previous studies have shown that oophorectomy is feasible in 85% of attempted vaginal hysterectomies and that the likelihood of oophorectomy increases with surgical experience (25–27). Moreover, our concomitant oophorectomy rate of 39% (3,172/8,103) is comparable to that of other studies with predominantly abdominal hysterectomy (28,29).

Women in whom both ovaries were intact had a higher risk of subsequent oophorectomy. This difference was statistically significant even after adjusting for age. In contrast, an uncontrolled retrospective study using ultrasound surveillance reported a higher risk (7.6% compared with 3.5%) of subsequent oophorectomy in women with one intact ovary rather than both intact ovaries after hysterectomy (12). However, 78% of ovaries had normal histopathology, perhaps suggesting that the relationship between hysterectomy and reoperation was biased by surveillance procedures. Our study was not prone to this bias. The reason for this imbalance between unilateral and bilateral preservation may be related to the indication for hysterectomy during the index procedure. Unfortunately, a limitation of the

current analysis is that we do not have full information regarding indications for the subsequent oophorectomy.

Although prophylactic oophorectomy during hysterectomy reduces the risk of ovarian cancer (30), women may have an increased risk of cardiovascular disease, dementia, and osteoporosis and higher all-cause and cancer-specific mortality (4–7). These risks are highest for women undergoing oophorectomy before the age of 45 years and decline thereafter until the early sixth decade (7). Furthermore, after a median follow-up of 15 years, there was a 54% increase in osteoporotic fractures among postmenopausal women who had oophorectomy at a median age of 62 years (31). Conversely, the incidence of ovarian cancer increases with age, peaking at the age of 70 years (1). While there is an ongoing debate about the pros and cons of oophorectomy, it is our professional opinion that it would be prudent to offer prophylactic oophorectomy only to women older than 60 years who are undergoing benign hysterectomy. Women with known risk factors for ovarian cancer are in a different category and should be counseled concerning the benefits of prophylactic oophorectomy (9,32).

The large sample size with a median follow-up of 19.5 years (IQR, 9.6–28.9 years; range, less than 0.1–43.5 years) allowed for accurate estimates of the incidence of subsequent oophorectomy, as well as sufficient power for comparisons. The use of a referent group allowed us to estimate the true effect of hysterectomy on the incidence of oophorectomy as opposed to other factors. In this study, the referent group (women who had not undergone hysterectomy) was chosen from the same community and matched by age to the hysterectomy patients. Strictly speaking, therefore, we cannot draw conclusions about the incidence of oophorectomy in the referent group as a whole, but only in comparison to the cases.

Between 2000 and 2004 in the United States, 3 million women underwent hysterectomy (23); therefore, the question of ovarian preservation is an important public health issue. Some gynecologists suggest that the ovaries be removed at the time of hysterectomy to avoid the risk of future surgery. This appears to be an unfounded concern, and women can be reassured that the odds are low that they will require a subsequent oophorectomy. Women of all age groups should be thoroughly counseled regarding the risks and benefits of ovarian preservation.

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Figure 1.
The cumulative incidence of subsequent oophorectomy among women who underwent hysterectomy (cases) and age-matched referent women (referents) from the same community.

Table 1

Summary of Demographic and Clinical Characteristics in Cases and Referents

Characteristic	Hysterectomy Cases (n=4,931)	Age-Matched Referents (n=4,931)
Age at index date, year		
Mean (SD)	42.9 (11.7)	43.6 (12.1)
Median (IQR)	41 (36–47)	41 (36–48)
Range	11–93	11–93
Ovary status at index date, n (%)		
One intact	86 (1.7)	86 (1.7)
Both intact, but unilateral salpingo-oophorectomy with hysterectomy	929 (18.8)	0
Both intact	3,916 (79.5)	4,845 (98.3)
Type of hysterectomy, n (%)		
Vaginal	3,632 (73.7)	
Abdominal	1,263 (25.6)	
Other (laparoscopic)	36 (0.7)	
Indication for hysterectomy, n (%)		
Uterine leiomyomas	1,454 (29.5)	
Precancerous condition	1,162 (23.6)	
Uterine or vaginal prolapse	903 (18.3)	
Menstrual disorders	848 (17.2)	
Endometriosis	338 (6.8)	
Inflammatory disease of pelvic organs	138 (2.8)	
Other	67 (1.4)	
Menopausal disorders	21 (0.4)	

SD, standard deviation; IQR, interquartile range.

Table 2
Cumulative Incidence of a Subsequent Oophorectomy Among the Hysterectomy Cases, Separately by Level of Ovarian Preservation

Ovarian Preservation at the Time of Hysterectomy	Number of Patients With Subsequent Oophorectomy	Cumulative Incidence of Subsequent Oophorectomy by Years After the Index Date, % [*]						
		2	5	10	15	20	25	30
One ovary intact (n=1,015)	34	1.2	1.7	2.8	3.2	4.0	4.0	4.0
Both ovaries intact (n=3,916)	281	0.7	1.9	3.7	5.3	6.8	8.8	10.6

^{*} The cumulative incidence of a subsequent oophorectomy is significantly different between the 2 groups (hazard ratio, 2.15; 95% confidence interval, 1.51–3.07; $P<.001$; based on a Cox model fit on an age scale).